9:15

PLATELET ACTIVATING FACTOR IS AN IMPORTANT MEDIATOR OF MYOCARDIAL REPERFUSION INJURY

Gary L. Schaer MD FACC, Tony L. Hursey BS, Daniel A. Rowan MD, David R. Campbell MD, Christian M. Heesch MD, Nancy Manabat BS, Joseph E. Parrillo MD. Rush Medical College, Chicago IL

Platelet activating factor (PAF) is a proinflammatory mediator released during myocardial ischemia. To determine if PAF is important in reperfusion (RP) injury, closed chest dogs underwent 90 min occlusion of the LAD (angioplasty balloon) and 3 days of RP. The PAF antagonist BN50739 (5 mg/kg iv; n=10) was given 15 min before RP and q12 hrs x 24 hrs post-RP; controls (n=8) received vehicle. Anterolateral ejection fraction (EF) was assessed by contrast ventriculography before LAD occlusion (baseline) and after 3 days of RP. The area at risk (AR) was defined by injection of monastral blue dye during a repeat LAD occlusion on day 3. The area of necrosis (AN) was measured from LV slices unstained by TTC. PAF inhibition was sustained for 36 hrs post-RP (by ex vivo PAF-induced platelet aggregation). BN50739 produced no adverse effects; collateral blood flow (microspheres) and rate-pressure product were similar.

	AR/LV	AN/AR	EF-baseline	EF-day 3
CONTROL	31±4% $_{NS}$	38±3% $_{p<.05}$	35±3% $_{NS}$	19±2%* $_{NS}$
BN50739	31±5%	29±3%	35±3%	16±2%*

[Data are mean±SEM; * p<0.05 vs baseline]

Conclusions: 1) PAF-inhibition reduces myocardial infarct size but does not significantly improve regional LV function 3 days post-RP. 2) These data suggest that PAF is an important mediator in the pathogenesis of myocardial reperfusion injury.

9:30

INHIBITION OF MYOCARDIAL PRODUCED LEUKOTRIENES D4, E4 IMPROVES CORONARY FLOW AND FUNCTIONAL RECOVERY IN ISOLATED CRYSTALLOID PERFUSED RAT HEARTS

C. Chin Lee, Robert F. Appleyard, John G. Byrne, Jeffrey M. Fleetwood, Lawrence H. Cohn. Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Leukotrienes D4,E4 (LTs) are potent coronary vasoconstricters. This study investigated the role of cardiac synthesized LTs in myocardial reperfusion injury. Increased cardiac synthesis of LTs was first demonstrated in isolated, crystalloid-perfused rat hearts subjected to 2hrs global ischemia at 15C (N=3). Postischemic LT production was elevated compared to preischemic values (170 vs 117pg/.1ml). LT content were analysed by radioimmunoassay. Next,the effects of LT inhibition on coronary flow and ventricular function using a LTD4,E4 receptor antagonist,LY171883,were assessed. After baseline measurements, hearts were arrested with standard postassium cardioplegia (C) (N=6) or C plus LY171883 ($3X10^{-6}$M) (D) (N=6) for 2hrs hypothermic global ischemia,followed by 30min reperfusion. Percent recovery of coronary flow(CF),cardiac output(CO) heart rate(HR),stroke work(SW) and coronary vascular resistance(CVR) were determined from baseline and post-ischemic measurements (mean±SD).

Group	CF	CO	HR	SW	CVR
C	53.3±6.2	49.7±4.9	93.5±10.2	53.7±6.3	181.1±28.4
D	81.7±6.9	78.6±6.4	96.0±6.4	82.3±10.7	121.2±13.4
P value	0.0001	0.0001	NS	0.0002	0.0009

These results demonstate that(1)LTs are endogencusly produced, with increased production after ischemia and(2)inhibition with a receptor antagonist improves coronary flow and functional recovery. Cardiac derived LTs partly control coronary flow and increased production may be an integral component of myocardial reperfusion injury.

9:45

U74006F DECREASES NECROSIS AND ENHANCES FUNCTIONAL RECOVERY AFTER ISCHEMIA/REPERFUSION IN ISOLATED RABBIT HEARTS

FRANK P. CARREA, EDWARD J. LESNEFSKY, AND LAWRENCE D. HORWITZ, Univ. of Colorado Health Sciences Center, Denver, CO

Lazaroids are a class of synthetic steroids which through inhibition of lipid peroxidation diminish central nervous system injury in experimental models. Since some aspects of myocardial ischemia/reperfusion injury may be mediated by this mechanism, we have chosen to apply U74006F (21-Aminosteroid), a potent, lipophilic, non-mineralocorticoid, steroid inhibitor of lipid peroxidation to an isolated rabbit heart model of "stop-flow"-reperfusion. Twenty-two New Zealand White rabbits (2.9±0.5 kg) received either U74006F 10 mg/kg i.v. (n=11) or 4 ml 0.01 N HCl vehicle i.v. (n=11) ten minutes prior to excision of the heart. The hearts were retrogradely perfused in an isovolumic fashion on a Langendorf apparatus with Krebs-Henseleit solution and underwent 30 minutes of "stop-flow" followed by 30 minutes of reperfusion. During reperfusion, CPK release was lower in the U74006F group (30 minutes of reperfusion: U74006F=31.2±5.6 U/min, vehicle=47.8±5.4 U/min, p<.01). Additionally, marked improvement in peak positive dP/dT (30 minutes of reperfusion: U74006F=786±66 mm Hg/sec, vehicle=523±102 mm Hg/sec, p<.01) and developed pressure (30 minutes of reperfusion: U74006F=42.3±3 mm Hg, vehicle=26.5±6 mm Hg, p<.01) were demonstrated in the U74006F group. These data suggest that treatment with U74006F results in less myocardial necrosis and improved early recovery of myocardial function. This may occur through protection against lipid peroxidation.

Wednesday, March 6, 1991
10:30AM–12:00NOON, Room 313, East Concourse
Prognosis After Myocardial Infarction II

10:30

PROGNOSIS OF PATIENTS WITHOUT MYOCARDIAL NECROSIS AFTER THROMBOLYTIC THERAPY: A TIMI II DATA BANK STUDY

Frank V. Aguirre, Harvey Serota, Robert P. McMahon, George Sopko, Rachel E. Solomon, Bernard R. Chaitman, Eugene Braunwald, and TIMI Investigators. St. Louis University School of Medicine, St. Louis, MO

The outcome of rt-PA therapy in patients with prolonged rest angina who present with ST segment elevation has not been well studied. The TIMI II trial assigned 3,339 patients (pts) with suspected acute myocardial infarction (MI) within 4 hours of symptom onset to an invasive or conservative strategy. In this report, we compared the 3-week and 1-year incidence of death and new MI in 102 pts presenting with chest pain ≥ 30 min., ST segment elevation, absence of serial Q wave changes, and serial CK values < 2 x upper limit of normal (group 1) to 3,237 pts with confirmed MI (group 2). All pts were treated with rt-PA, heparin, and aspirin. Death and MI rates were assessed at 3-weeks and 1-year after admission.

	Death (%)		New MI (%)	
Subgroup	3-Weeks	1-Year	3-Weeks	1-Year
Group 1 (n=102)	0.0	1.1	10.1	11.1
Group 2 (n=3,237)	4.7	7.3	6.3	9.6
p value	0.03	0.02	0.15	0.60

The revascularization rate 3-weeks post admission in pts randomized to the conservative strategy was similar in both groups (p=0.12). Thus, pts with prolonged chest pain and ST segment elevation who do not develop myocardial necrosis have a low 1-year mortality, less than pts with confirmed MI (p=0.02). There remains a high incidence of subsequent myocardial infarction in both group 1 and 2 pts treated with rt-PA, heparin, and aspirin.